

Factors Influencing Survival After Resection for Ductal Adenocarcinoma of the Head of the Pancreas

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Background and Objectives: Recent reports have demonstrated improvement in the 5-year actuarial survival for patients with resected ductal adenocarcinoma. The purpose of this study is to determine the factors favoring long-term survival after pancreaticoduodenectomy.

Methods: Between 1974 and 1995, 75 patients with pancreatic head carcinoma underwent pancreaticoduodenectomy in our department.

Results: Overall postoperative mortality rate was 5.3% and morbidity was 24%. Median survival following resection was 17 months. Estimated 1-, 2-, and 5-year survival rates were 68%, 46.7%, and 18.7%, respectively. Five-year survival was greater for node-negative than for node-positive patients (41.7% vs. 7.8%, $P < 0.001$) and for smaller (<3 cm) than for larger tumors (33.3% vs. 8.8%, $P < 0.006$). The 5-year survival in patients with negative margins ($n = 60$) was 23.3%, whereas no patient with positive margins ($n = 15$) survived at 13 months ($P < 0.001$). Multivariate analysis, performed by the Cox proportional hazards model, indicated that margin status, lymph node metastasis, tumor size, and poor histological differentiation were independent predictors of poor survival.

Conclusions: Five-year survival for patients undergoing pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas was 18.7%. Survival was greater in the group of patients with negative lymph nodes, tumor size <3 cm, and negative margin status.

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KEY WORDS: pancreatic cancer; pancreaticoduodenectomy; lymph node metastases; tumor size; margin status

INTRODUCTION

For the majority of patients, ductal adenocarcinoma of the pancreas remains a lethal disease. Almost all patients die within 2 years of diagnosis [1]. Nonspecificity of symptoms, advanced disease at presentation, and lack of effective adjuvant and systemic therapy explain this grim prognosis. Currently, surgical resection offers the only chance for long-term survival. The predominant site for ductal adenocarcinoma is the head of the gland, requiring a pancreaticoduodenectomy for removal. Since Whipple and colleagues [2] introduced pancreaticoduodenectomy for the treatment of ampullary tumors, the indications for this procedure have been broadened to include ductal

pancreatic cancer. The classic operation has gone through numerous modifications to specifically tailor it for better results with the treatment of ductal pancreatic cancer, either by preserving the pylorus [3–7], by performing a total pancreatectomy [8–10], or by extending

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resection margins to include a lymphadenectomy [11–15] or an en bloc resection of peripancreatic tissues [16–20].

Based on results from the 1960s, 1970s, and early 1980s, many authors argued that excessive mortality and morbidity associated with surgical resection coupled with the lack of long-term survivors indicated that pancreatic resection should be abandoned for ductal cancer [20–23]. However, recent reports from other referral centers have demonstrated that pancreatic resection can be performed with mortality rates of <5% [24–33]. In addition, 5-year actuarial survival rates after resection have been reported in excess of 20% [25,29,31,32]. These results suggest that resection is justified and may offer the possibility of cure to a significant proportion of patients. In contrast, other authors have failed to demonstrate improved survival [34–36]. In fact, in some reports, there were no 5-year survivors [37].

These conflicting results prompted us to critically review the clinicopathological characteristics of our patients who were resected for ductal adenocarcinoma of the pancreas between 1974 and 1995, to define the true 5-year survival rate at our local setting and the factors influencing long-term survival.

MATERIALS AND METHODS

Between January 1974 and January 1995, 336 patients were admitted to our department with a histologically confirmed diagnosis of ductal adenocarcinoma of the pancreas. There were 198 male patients and 138 female patients. Ages ranged from 36 to 78 years, with a mean of 67 years. The head of the gland was the predominant tumor site ($n = 235$), followed by body ($n = 59$) and tail ($n = 42$). Seventy-five (32%) patients with pancreatic head adenocarcinoma underwent surgical resection. In this group, ages ranged from 40 to 76 years, with a mean of 65 years. Fifty patients were male and 25 were female.

The standard operation for resectable cancer was Whipple's procedure and included resection of the lymph nodes intimately associated with the pancreatic head as well as those along the distal bile duct (R1; $n = 61$). Among patients selected for good performance status ($n = 14$), the resection included an extensive lymph node dissection (R2), which skeletonizes the hepatic arteries, the celiac axis, the superior mesenteric artery, or the retroperitoneal tissue surrounding the inferior vena cava and aorta.

A jejunal loop was used for reconstruction, with end-to-end "dunking" pancreatojejunostomy or end-to-side anastomosis, which sews the pancreatic duct directly into a small opening in the jejunum. An end-to-side choledochojejunostomy was constructed on the same jejunal loop.

In this study, the original clinical and pathological reports of all patients were reviewed to determine some

variables: sex, age, blood transfusion, type of resection (R1 or R2), tumor size, grade (well, moderately, or poorly differentiated), extrapancreatic spread (present or absent), nodal metastases, margin status, and stage (using the TNM system). The purpose of this study was to critically determine the factors influencing survival in patients with potentially resectable pancreatic head carcinoma.

Operative mortality was defined as any death occurring within 30 days of the date of operation. Estimated survival rate was determined from the date of surgical resection according to the Kaplan-Meier product limit method of life-table analysis, and operative death was included [38]. Differences in survival between groups were compared with the log-rank test. $P < 0.05$ was considered to indicate a significant difference. Multivariate analysis was performed with the Cox proportional hazards model.

RESULTS

The median duration of operation was 6.0 hr (range 3.0 to 9.0, mean 6.2). The median intraoperative blood loss was 800 ml (range 400 to 1000 ml). All patients received a blood transfusion in the postoperative period; 44 (58.6%) patients received <2 units of red blood cells and 31 (41.3%) patients received >3 units. The median amount of the blood transfused was 2 units of packed red cells (range 1 to 4 units).

Major postoperative complications occurred in 18 of 75 patients, for an overall operative morbidity of 24%. Four patients developed postoperative bleeding and required reoperation. Bleeding occurred from the cut edge of the pancreatic remnant in 2 patients and the pancreatic resection bed in 2 patients. Two patients developed leaks at the choledochojejunostomy with biliary fistulas that resolved spontaneously after 4 and 5 week, respectively. Two patients developed an intraabdominal abscess, requiring percutaneous drainage. Seven patients developed a pancreatic fistula, defined as persistent drainage >50 ml of amylase-rich fluid per day for >2 weeks. Five of these fistulas closed spontaneously. One patient required reoperation for persistent fistula. Pulmonary embolism, myocardial infarction, and cardiac arrhythmia occurred in 1 patient each.

Four of the 75 patients died within 30 days of operation, for an overall operative mortality of 5.3%. Three of these 4 patients died of cardiopulmonary events. The other patient, with a pancreatic fistula, developed an intraabdominal abscess with sepsis and multiple organ failure.

Patients were stratified according to stage using the TNM classification. In stage I ($n = 24$), there were 3 patients with T1aN0M0 disease, 9 patients with T1bN0M0, and 12 patients with T2N0M0 disease. By contrast, in stage III ($n = 51$), there were 45 and 6

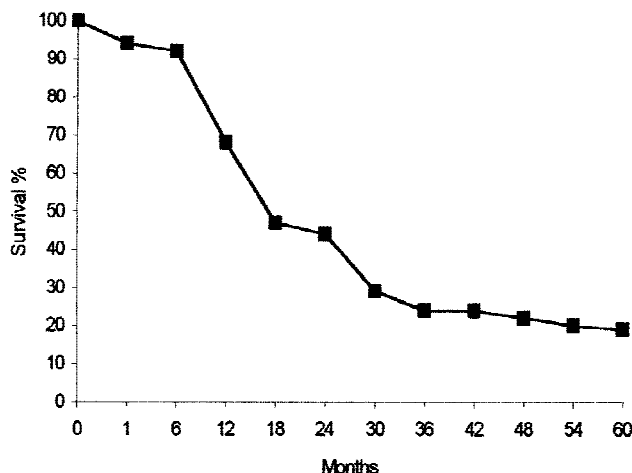


Fig. 1. Actuarial survival rate in 75 patients with adenocarcinoma of the head of the pancreas following pancreaticoduodenectomy.

patients with T2N1M0 and T3N1M0 disease, respectively.

Tumor size was recorded for 67 patients; the median was 3.8 cm (range 1.0 to 12 cm, mean 4.0 cm). Thirty-three patients (49%) had tumors <3 cm in diameter.

Using Broder's grading, 50 patients (66.7%) had grade 3 tumors and 21 patients (28%) had grade 2 tumors; only 4 patients (5.3%) had well-differentiated grade 1 ductal adenocarcinoma. Histological review demonstrated tumor invasion into the duodenum in 21 patients (28%) and extensive perineural invasion in 10 patients (13.3%). The number of lymph nodes resected in the specimens ranged from 6 to 34 (mean 16 lymph nodes). Of the 75 patients, 24 (32%) had negative lymph nodes in the resected specimens. In 51 patients (68%), metastatic involvement of lymph nodes within the resected specimen was noted. The R1 dissection was performed in 39 patients with lymph node metastases and 22 patients with negative lymph nodes. By contrast, the R2 resection was performed in 12 patients with lymph node metastases and in 2 patients with negative lymph nodes. The number of positive lymph nodes in the resected specimens ranged from 6 to 22 (mean 12 lymph nodes).

Median survival following resection was 17 months (range 0 to 79). Estimated 1-, 2-, 3-, and 5-year survival rates were 68%, 46.7%, 24%, and 18.7%, respectively (Fig. 1). There were 14 5-year survivors. There were no significant differences in survival based on age ($P = 0.75$) or gender ($P = 0.81$). No significant improvement in survival was seen when blood transfusions of ≤ 2 units and >2 units, given preoperatively, were compared ($P = 0.74$) (Table I).

Stage significantly affected survival, with 5-year survival rates of 41.7% and 7.8% for stages I ($n = 24$) and III ($n = 51$), respectively. When stratified according to the various subsets of these 2 stages, the 5-year survival rates for patients with T1aN0M0 ($n = 3$), T1bN0M0

($n = 9$), and T2N0M0 ($n = 12$) disease were 100%, 43%, and 23.1%, respectively. By contrast, the 5-year survival rate for patients with T2N1M0 ($n = 45$) was 8.9% and no patient with T3N1M0 ($n = 6$) disease survived at 5 years.

The histological grade of the tumor significantly affected survival when well-differentiated tumors were compared with poorly differentiated tumors ($P = 0.001$) and poorly differentiated tumors were compared with moderately differentiated tumors ($P < 0.001$). The effect of tumor differentiation was not correlated with survival when moderately and well differentiated tumors were compared ($P = 0.21$).

The absence of nodal metastases in the operative specimens conferred a definitive survival advantage. Patients with positive lymph nodes ($n = 51$) had a median survival of 13 months (range 0 to 61), and patients with negative lymph nodes ($n = 24$) had a median survival of 33 months (range 5 to 79). Estimated survival rates for patients with positive lymph nodes at 1, 2, 3, and 5 years were 58.8%, 31.4%, 11.8%, and 7.8%, respectively, compared with 87.5%, 79.2%, 50%, and 41.7% ($P < 0.001$), respectively, for patients with negative lymph nodes (Fig. 2). There were 4 5-year survivors in the group of patients with lymph node metastases; 2 patients had the extensive lymph node dissection (R2) and two others had the R1 procedure. In patients with lymph node metastases undergoing R1 resection ($n = 39$), the 1-, 2-, and 5-year survival rates were 48.7%, 23.1%, and 5.1%, respectively. Whereas in patients with positive lymph nodes undergoing R2 resection ($n = 12$), the 1-, 2-, and 5-year survival rates were 91.7%, 58.3%, and 16.7%, respectively ($P = 0.02$).

The diameter of the tumor is also an important predictive factor of survival (Fig. 3). Patients with tumor <3 cm ($n = 33$) had a median survival of 18 months, whereas patients with tumor >3 cm had a median survival of 11 months ($n = 34$). Estimated 1-, 2-, 3-, and 5-year survivals in the patients with tumor <3 cm were 81.8%, 48.5%, 39.4%, and 33.3%, respectively, compared with 50%, 41.2%, 11.8%, and 8.8%, respectively, for patients with tumor >3 cm ($P = 0.006$).

As expected, the status of resection margins in specimens also proved to be a highly significant factor predicting survival (Fig. 4). Patients resected with negative margins (curative resection, $n = 60$) had a median survival of 26 months and an actuarial 5-year survival rate of 23.3%, whereas those resected with positive margins ($n = 15$) fared significantly worse; no patients survived 13 months, with a median survival of 9 months ($P < 0.001$).

Multivariate analysis was performed by the Cox proportional hazards model, to determine independent prognostic determinants of long-term survival. The probability values, hazard ratios, and confidence intervals for the

TABLE I. Factors Influencing Survival after Pancreaticoduodenectomy

Parameter (n)	Median survival (months)	5-year survival	Log-rank <i>P</i> value
Age (years)			
>65 (44)	16	22.5%	0.75
<65 (31)	17	16%	
Gender			
Male (50)	16	20%	0.81
Female (25)	17	16%	
Packed red cell transfusions			
<2 units (44)	16	22.6%	0.74
>2 units (31)	17	15.9%	
Lymph node status			
Negative (24)	33	41.7%	<0.001
Positive (51)	13	7.8%	
Tumor size (cm)			
<3 (33)	18	33.3%	0.006
>3 (34)	11	8.8%	
Margin status			
Negative (60)	26	23.3%	0.001
Positive (15)	9	0	
Histological grade			
Well-differentiated (4)	54	75%	<0.001
Moderately differentiated (21)	33	42.9%	
Poorly differentiated (50)	16	4%	
Type of resection in patients with lymph nodes metastases			
R1 (39)	11	5.1%	0.02
R2 (12)	26	16.7%	

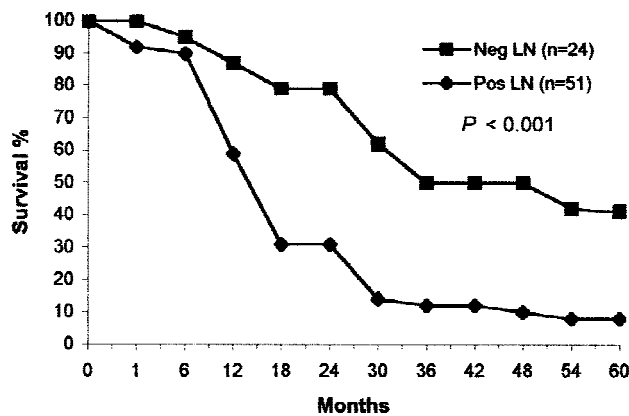


Fig. 2. Actuarial survival rate according to lymph node involvement in 75 patients with head pancreatic adenocarcinoma following pancreaticoduodenectomy. Neg, negative; Pos, positive; LN, lymph node.

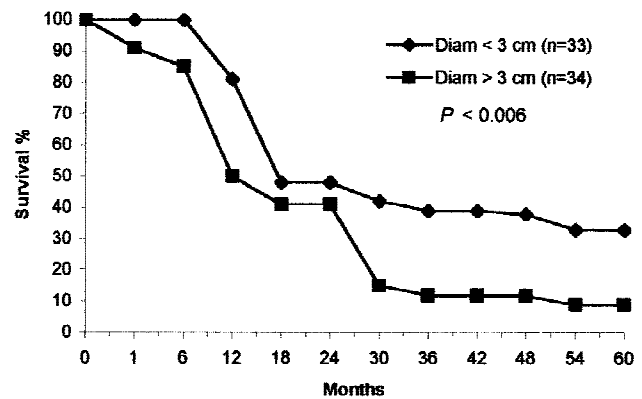


Fig. 3. Actuarial survival according to tumor size in 67 patients with head pancreatic adenocarcinoma following pancreaticoduodenectomy. Diam, diameter.

final multivariate model are listed in Table II. The presence of positive resection margins was the strongest independent predictor of decreased survival (hazard ratio = 2.29, $P = 0.000$). Lymph node metastasis (hazard ratio = 1.17, $P = 0.0002$), tumor size >3 cm (hazard ratio = 0.73, $P = 0.009$), and poor histological differentiation (hazard ratio = 1.14, $P = 0.0001$) also were independent predictors of poor survival. The most favorable subset was 17 patients who had negative resection margins, negative lymph nodes, and tumor size <3 cm. Their 5-year survival rate was 52.9%.

DISCUSSION

During the 1960s and 1970s, some authors suggested that pancreaticoduodenectomy for pancreatic cancer should be abandoned because of high complication and mortality rates and low survival rates [20–23]. In recent years, surgical treatment of adenocarcinoma of the head of the pancreas has been associated with falling postoperative morbidity and mortality rates and long-term survival [24–33]. Geer and Brennan [29] reported an actuarial survival of 24% at 5 years for 146 patients who had resection; no 5-year survivors were seen in 653 patients

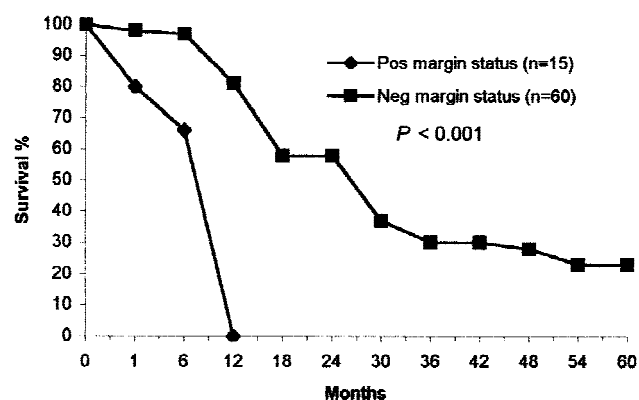


Fig. 4. Actuarial survival according to margin status after pancreaticoduodenectomy in 75 patients with head pancreatic adenocarcinoma. Pos, positive; Neg, negative.

TABLE II. Multivariate Analysis of Prognostic Factors

Variable	Hazard ratio	95% Confidence limits	P value
Positive resection margins	2.29	1.91–2.67	0.0000
Tumor size >3 cm	0.73	0.45–1.01	0.009
Positive lymph nodes	1.17	0.86–1.48	0.0002
Pore histological differentiation	1.14	0.86–1.42	0.0001

who did not undergo resection. Yeo and colleagues [27] reported a 21% actuarial 5-year survival in a group of 201 patients undergoing resection for adenocarcinoma of the pancreas at Johns Hopkins Hospital. Of 201 patients, 57 (28%) had negative lymph nodes. The median and 5-year survival rates in these node-negative patients were 28 months and 36%, respectively, which was significantly longer than for the node-positive patients. In the data from Johns Hopkins Hospital, DNA content of the pancreatic cancer cells, as determined by image cytometry, was a highly significant determinant of survival. Patients with diploid tumors had median and 5-year survival rates of 24 months and 39%, respectively, which was significantly longer than observed in patients with aneuploid tumors. Willet and colleagues [39] emphasize the importance of negative pathological margins; overall, 5-year actuarial survival was 13%, but in the group with negative margins (35/72 patients), this was significantly improved to 22%. Similar results were demonstrated by Trede and associates [25], who reviewed the Mannheim Surgical Clinic's experience between 1972 and 1989. In this retrospective study, the overall actuarial 5-year survival rate was 24%; when the tumor was excised both macroscopically and microscopically, actuarial survival increased to 36% for this subgroup of 36 patients. Delcore and colleagues [40], reviewing the University of Kansas Medical Center experience between 1970 and 1995, reported an actuarial 5-year survival of 20% for 100 patients undergoing pancreaticoduodenectomy for

ductal adenocarcinoma of the pancreas. The authors suggested the importance of negative lymph nodes. Estimated survival for patients with positive lymph nodes at 5 years was 6% compared to 35% for patients with negative lymph nodes.

In contrast, Nitecki and colleagues [34], reviewing the Mayo Clinic experience between 1981 and 1991, reported an actuarial survival of 6.8% after resection. Complete resection with negative lymph nodes and no perineural or duodenal invasion resulted in a 5-year survival of 23%. However, this subset accounted for only 40% of their patients. Conlon and colleagues [36] reported an actuarial 5-year survival of 10.2% for 118 patients with pancreatic cancer undergoing resection. Large multicenter studies from Europe and the United States also have reported actuarial 5-year survival rates between 8% and 12% [35,41,42]. Our actuarial 5-year survival rate was 18.7%.

The presence of lymph node metastases has a significant correlation with long-term survival. In this study, patients with negative lymph nodes had an actuarial 5-year survival of 41.7%, whereas patients with lymph node metastases had an actuarial 5-year survival rate of 7.8% ($P < 0.001$). These findings support results from several different institutions [28,29,40] and confirm the presence of lymph node metastases as an important predictor of poor survival for patients with adenocarcinoma of the pancreas. The usefulness of performing an extended lymphadenectomy and retroperitoneal soft-tissue clearance in conjunction with a pancreaticoduodenal resection in the treatment of ductal adenocarcinoma of the head of the pancreas is still unknown. Published studies suggest a benefit for the procedure in terms of better long-term survival rates; however, these studies were retrospective [11–14]. The lack of randomized prospective trials involving a sufficient number of cases does not allow us to make any final conclusions. The only controlled data, from an Italian multicenter study, suggested that extended lymphadenectomy improved prognosis, not in the whole population of resected patients but only in a subgroup of patients with lymph node involvement [15].

In our experience, the presence of lymph node metastases did not preclude the possibility of meaningful survival. Four patients with positive lymph nodes remain alive 5 years after resection without recurrence. In 2 patients, we performed an extensive lymph node dissection (R2), including the lymph nodes at the superior body, inferior body, celiac axis, common hepatic duct, mid-colic region, paraaortic region, and superior mesenteric vessels. In the other 2 patients, an R1 procedure was performed. The 1-, 2-, and 5-year survival rates in patients with lymph node metastases undergoing the R1 procedure ($n = 39$) were 48.7%, 23.1%, and 5.1%, respectively, whereas, the 1-, 2-, and 5-year survival rates of patients with negative lymph nodes undergoing the R2

resection ($n = 12$) were 91%, 58.3%, and 16.7%, respectively. The difference was statistically significant ($P = 0.02$), but this is likely related to accurate selection of patients undergoing R2 dissection. A randomized prospective trial of R1 dissection versus R2 dissection is needed to evaluate the best procedure in patients with pancreatic head adenocarcinoma.

Occasional long-term survivors with positive lymph nodes have been reported [25,29]. Consequently, we believe that all patients with pancreatic head carcinoma should undergo surgical resection even in the presence of lymph node metastases since it is now possible to cure a significant number of patients (7.8% actuarial 5-year survival), and the operation can now be performed with low enough morbidity and mortality to warrant its use as a palliative procedure. In the presence of lymph node metastases, pancreaticoduodenectomy offers good palliation and meaningful survival. In the absence of lymph node metastases, surgical resection offers encouraging long-term survival rates and a chance of cure.

Tumor diameter is also an important predictor of survival [28,29,43]. In our experience, of 67 patients for whom this measurement was available, 33 (49%) had tumors <3 cm in diameter. Median and 5-year survival rates in these patients were 18 months and 33.3%, respectively. When the tumor diameter exceeded 3.1 cm, median and 5-year survival rates were 11 months and 8.8%, respectively ($P = 0.006$).

The status of the resection margins is another highly significant factor predicting survival [28,44,45]. Our specimens were routinely examined for microscopic tumor involvement at the pancreatic neck, uncinate process, retroperitoneal soft tissue, and duodenal and bile duct margins. As expected, the worst prognosis was observed for 15 patients in whom microscopically and macroscopically incomplete resections were done. Median survival in these patients was 9 months, and no patient survived at 5 years. Patients whose resected specimens had negative margins ($n = 60$) had a median survival of 26 months and an actuarial 5-year survival rate of 23.3% ($P < 0.001$).

Multivariate analysis of survival, with covariates of tumor size, lymph node involvement, grading, and margin status, was performed by the Cox proportional hazards model to determine independent prognostic determinants of long-term survival. The presence of positive resection margins was the strongest independent predictor of decreased survival. Lymph node metastasis, tumor size >3 cm, and poor histological differentiation also were independent predictors of poor survival.

Five-year survival for patients undergoing pancreatic resection for lesions deemed to be clinically curable intraoperatively and histologically confirmed to be ductal adenocarcinoma of the head of the pancreas was 18.7%. Survival was greater in the group of patients with nega-

tive lymph nodes (41.7%), tumour size <3 cm (33.3%), and negative margin status (23.3%).

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